oligosaccharides, or in vitro evolution, and wherein said selected drugs bind to the selected synthetic receptors with lower affinity than to the drugs' pathophysiologic receptors;

(b) specifically binding the selected drugs to the selected synthetic receptors so that a multi-prodrug complex is produced, said multi-prodrug complex comprising the selected drugs and the selected synthetic receptors specifically bound via a saturable, noncovalent interaction between the selected drugs and the synthetic receptors that can be competitively inhibited by structural analogs of the selected drug; and

(c) administering the multi-prodrug complex to an organism so that the selected drugs dissociate from the synthetic receptors and bind to the drugs' pathophysiologic receptors.

REMARKS

At the outset, Applicant thanks Examiner Ware for the courtesy of the Telephone Interview conducted on April 10, 2001. Applicant is filing this Preliminary Amendment to address issues discussed during this Telephone Interview with respect to differences between the instant invention and Morgan Jr. et al. (U.S. Patent 5,106,951).

Claims 13-29 are pending in the instant application. Claims 13-29 have been rejected as being anticipated and/or obvious over the teachings of Morgan, Jr. et al. (U.S. Patent 5,106,951). Claims 13, 14, 16, 18, 20, 22, 24, 26 and 28 have been amended in this Preliminary Amendment. No new matter has been added by these amendments. Entry of these amendments is therefore respectfully requested.

As discussed during the interview of April 10, 2001, the prior art reference by Morgan, Jr. et al. (U.S. Patent 5,106,951) discloses an antibody-csDBM-drug conjugate wherein the csDBM is defined as a class of chemicals designed to fit the drug by combining multiple non-covalent interactions between functional groups on the drug and opposing functional groups on the csDBM (see Abstract). As taught at col. 4, lines 61-67 of the '951 patent, the immunoconjugates of Morgan Jr. et al. comprise a targeting protein such as an antibody or antibody fragment, a moiety termed a drug binding molecule of complementary structure (abbreviated csDBM) which is covalently bound to the antibody or carrier, and a drug noncovalently complexed to the csDBM. In another configuration, as taught at col. 4, line 67, through col. 5, line 2, the drug is first bound through covalent bonds to an antibody or carrier and then complexed with a csDBM. The csDBM is further

defined at col. 5, line 64 through col. 6, line 17, as a molecule that has a form opposite and complementary to that of a drug, or functionalities that are opposite and complementary in structure to a drug molecule. A preferred example is taught where the csDBM and the drug have a similar planar ring structure, but with opposing functionalities. Examples of opposing functionalities on the csDBM include groups for hydrogen and ionic binding and other noncovalent interactions, with or without electron poor or electron rich groups on the csDBM to increase the pi binding. It is also taught at this section that the csDBM are sterically oriented in proper three-dimensional alignment such that the functional group on the drug interacts with the opposing functional group on the csDBM in proper steric orientation.

It is stated at col. 7, lines 31-39, of the '951 patent that the:

> invention is a csDBM, a csDBM/drug complex, a carrier csDBM/drug conjugate, a targeting protein/csDBM/drug conjugate, a targeting protein/carrier/csDBM/drug conjugate, a targeting protein/carrier/drug/csDBM complex and a method of designing or producing a csDBM wherein a csDBM can be identified in nature or synthesized that will undergo multiple, non-covalent interactions with a drug.

Thus, quite clearly the csDBM is a required element of the invention of Morgan Jr. et al.

In contrast, as also discussed during the April 10th Interview, the prodrug complexes of the instant invention do not involve a csDBM. Nor do the complexes of the present invention involve covalently binding a drug to an antibody or carrier and then complexing the drug with a csDBM. Thus, contrary to the Examiner's suggestion in the Interview Summary sheet of April 24, 2001, the synthetic receptors of the present invention are different from the antibodies of Morgan Jr. et al.

Not in claims

As taught in the specification at page 7, line 25-35, in the prodrug and multi-prodrug complexes of the present invention, a drug molecule is **specifically bound**, meaning a saturable, noncovalent interaction between a ligand and a receptor that can be competitively inhibited by structural analogs of the ligand, to a synthetic receptor. Also, at almost every point in the instant specification where the interaction of the synthetic receptor with the drug molecule is discussed, it is made clear that specific binding is required. See particularly page 5, lines 6, 7, 11, 16-17, 18-19, 22, 23 and 28, page 6, line 29, page 7, line 12, page 10, lines 30 and 32, page 12, line 25 and 29, page 13, line 24 and 26, and page 14, line 8-9. In fact, Applicant included the phrase "specifically binds" in the claims as originally filed. Further, the term "synthetic receptor" is defined in the instant

specification as referring to any naturally occurring, recombinant, biologically produced or synthetic ligand or receptor which is designed, selected or engineered to **specifically bind** a drug. In addition, at page 10, lines 6-11, it is taught that "synthetic receptors are identified through iterative screening and selection for specific binding attributes . . ." Thus, the criticality of a drug molecule **specifically binding**, meaning a saturable, noncovalent interaction between a ligand and a receptor that can be competitively inhibited by structural analogs of the ligand, with a synthetic receptor in the prodrug complexes and multi-prodrug complexes of the present invention is clearly evidenced by the teachings of the specification.

Specific binding, meaning a saturable, noncovalent interaction between a ligand and a receptor that can be competitively inhibited by structural analogs of the ligand, between a drug molecule and a synthetic receptor is clearly different from Morgan Jr. et al. which teaches either

1) use of a drug binding molecule of complementary structure which is covalently bound to the antibody or carrier and noncovalently complexed to a drug molecule the csDBM; or

2) use of a drug which is covalently bound to an antibody or carrier and complexed with a csDBM.

In an earnest effort to advance the prosecution of this case and to clarify distinguishing features of the present invention from the teachings of Morgan Jr. et al., Applicant has amended the claims in accordance with the above outlined teachings of the specification to state that the drug molecules and synthetic receptors of the prodrug or multi-prodrug complexes are specifically bound via a saturable, noncovalent interaction between the selected drug and the synthetic receptor that can be competitively inhibited by structural analogs of the selected drug. Since Morgan Jr. et al. neither teaches nor suggests prodrug complexes comprising a synthetic receptor specifically bound to a drug molecule via a saturable, noncovalent interaction between the selected drug and the synthetic receptor that can be competitively inhibited by structural analogs of the selected drug, this reference neither anticipates nor renders obvious the invention as now claimed.

Withdrawal of the pending rejections under 35 U.S.C. § 102(b) and 35 U.S.C. § 103(a) over Morgan Jr. et al. is therefore respectfully requested.

Claims 14 and 18 have also been amended to address the rejection under 35 U.S.C. § 112, second paragraph. The Examiner suggested that recitation of "a drug bound to a synthetic receptor selected to bind said drug by a method selected from . . ." in claim 14 was unclear as this may be understood to claim that these are methods by which the drug binds to a synthetic receptor rather than methods for identifying the synthetic receptor. Accordingly, claim 14 has been amended to clarify that the methods are used to identify (i.e. select) the synthetic receptor. Since similar language also appeared in claim 18, Applicant has also amended this claim to clarify that the methods are used to select the synthetic receptor. Withdrawal of the rejection under 35 U.S.C. § 112, second paragraph is therefore respectfully requested.

Applicant believes that this Preliminary Amendment overcomes all pending rejections of the instant application. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Attached hereto is a marked-up version of the changes made to

the specification and claims by the current amendment. The attached page is captioned "Version with Markings to Show Changes Made."

Respectfully submitted,

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Date: **May 3, 2001**

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims:

The following claims have been amended:

13. (amended) An immobilized prodrug complex comprising:

(a) a selected synthetic receptor;

(b) a selected drug ~~that binds~~ specifically bound to the synthetic receptor via a saturable, noncovalent interaction between the selected drug and the synthetic receptor that can be competitively inhibited by structural analogs of the selected drug, wherein the selected drug is specifically bound to the synthetic receptor with lower affinity than to the drug's pathophysiologic receptor so that the selected drug preferentially binds to the pathophysiologic receptor with no loss of efficacy of the selected drug; and

(c) a biologic or biocompatible structure to which the selected synthetic receptor or selected drug is immobilized.

14. (amended) A prodrug complex comprising a drug specifically bound to a synthetic receptor selected to bind to said drug via a saturable, noncovalent interaction between the selected drug and the synthetic receptor that can be competitively inhibited

by structural analogs of the selected drug, wherein said synthetic receptor is selected by a method selected from the group consisting of combinatorial selection, monoclonal antibody selection and antibody engineering, wherein said drug preferentially dissociates from the synthetic receptor and binds to a pathophysiologic receptor following administration of the prodrug complex to an organism.

16. (amended) A method of producing a prodrug complex comprising:

(a) selecting a drug to be delivered as a prodrug complex;

(b) selecting a synthetic receptor that specifically binds to the drug via a saturable, noncovalent interaction between the selected drug and the synthetic receptor that can be competitively inhibited by structural analogs of the selected drug, wherein said synthetic receptor is selected by at least one of combinatorial selection, screening and selection of antibodies, engineered antibodies, oligonucleotides or oligosaccharides, or in vitro evolution; and

(c) specifically binding the selected drug to the selected synthetic receptor to form a prodrug complex.

18. (amended) A multi-prodrug complex comprising at least two drugs specifically bound to at least two synthetic receptors via a saturable, noncovalent interaction between the drugs and the synthetic receptors that can be competitively inhibited by structural analogs of the drugs, wherein at least one of the synthetic receptors ~~is selected to bind~~ specifically bound to said drug is selected by a method selected from the group consisting of combinatorial selection, monoclonal antibody selection and antibody engineering, and wherein said drugs preferentially dissociate from the synthetic receptors and bind to pathophysiologic receptors following administration of the multi-prodrug complex to an organism.

20. (amended) A method of producing a multi-prodrug complex comprising:

(a) selecting at least two drugs to be delivered as a multi-prodrug complex;

(b) selecting at least two synthetic receptors that specifically bind to the selected drugs via a saturable, noncovalent interaction between the selected drug and the synthetic receptor that can be competitively inhibited by structural analogs of the selected drug, wherein at least one of the synthetic

receptors is selected by at least one of combinatorial selection, screening and selection of antibodies, engineered antibodies, oligonucleotides or oligosaccharides, or in vitro evolution; and

(c) specifically binding the selected drugs to the selected synthetic receptors to form a multi-prodrug complex.

22. (amended) A prodrug complex comprising:

(a) a synthetic receptor selected from the group consisting of drug receptors, transmitter receptors, autocoid receptors, cytokine receptors, antibodies, antibody fragments, molecular recognition units, engineered antibodies, antibody mimics, adhesion molecules, agglutinins, integrins, selectins, nucleic acids and biopolymers comprising nucleotides, saccharides, fatty acids, phenols, phosphates, sulfates, other organic monomers or nonbiologic monomers, wherein said synthetic receptor is selected by at least one of combinatorial selection, screening and selection of antibodies, engineered antibodies, oligonucleotides or oligosaccharides, or in vitro evolution; and

(b) a selected drug ~~that binds~~ specifically bound to the synthetic receptor via a saturable, noncovalent interaction between the selected drug and the synthetic receptor that can be competitively inhibited by structural analogs of the selected drug,

wherein the selected drug is specifically bound to the synthetic receptor with lower affinity than to the drug's pathophysiologic receptor so that the selected drug dissociates from the synthetic receptor and preferentially binds to the pathophysiologic receptor.

24. (amended) A method of enhancing delivery of a selected drug to a pathophysiologic receptor for said selected drug comprising:

(a) selecting a drug to be delivered as a prodrug complex and a synthetic receptor selected from the group consisting of drug receptors, transmitter receptors, autocoid receptors, cytokine receptors, antibodies, antibody fragments, molecular recognition units, engineered antibodies, antibody mimics, adhesion molecules, agglutinins, integrins, selectins, nucleic acids and biopolymers comprising nucleotides, saccharides, fatty acids, phenols, phosphates, sulfates, other organic monomers or nonbiologic monomers, wherein said synthetic receptor is selected by at least one of combinatorial selection, screening and selection of antibodies, engineered antibodies, oligonucleotides or oligosaccharides, or in vitro evolution, and wherein said selected drug binds to the selected synthetic receptor with lower affinity than to the drug's pathophysiologic receptor;

(b) specifically binding the selected drug to the selected synthetic receptor ~~to produce~~ so that a prodrug complex is produced, said prodrug complex comprising the selected drug and the selected synthetic receptor specifically bound via a saturable, noncovalent interaction between the selected drug and the synthetic receptor that can be competitively inhibited by structural analogs of the selected drug; and

(c) administering the prodrug complex to an organism so that the selected drug dissociates from the selected synthetic receptor and binds to the drug's pathophysiologic receptor.

26. (amended) A multi-prodrug complex comprising:

(a) at least two synthetic receptors, at least one of which is selected from the group consisting of drug receptors, transmitter receptors, autocoid receptors, cytokine receptors, antibodies, antibody fragments, molecular recognition units, engineered antibodies, antibody mimics, adhesion molecules, agglutinins, integrins, selectins, nucleic acids and biopolymers comprising nucleotides, saccharides, fatty acids, phenols, phosphates, sulfates, other organic monomers or nonbiologic monomers, wherein said synthetic receptors are selected by at least one of combinatorial selection, screening and selection of

antibodies, engineered antibodies, oligonucleotides or oligosaccharides, or in vitro evolution; and

(b) at least two selected drugs ~~that bind~~ specifically bound to the synthetic receptors via a saturable, noncovalent interaction between the selected drugs and the synthetic receptors that can be competitively inhibited by structural analogs of the selected drugs, wherein the selected drugs are specifically bound to the synthetic receptors with lower affinity than to the drugs' pathophysiologic receptors so that the selected drugs dissociate from the synthetic receptors and preferentially bind to their pathophysiologic receptors.

28. (amended) A method of enhancing delivery of selected drugs to pathophysiologic receptors for said selected drugs comprising:

(a) selecting at least two drugs to be delivered as a multi-prodrug complex and at least two synthetic receptors, at least one of which is selected from the group consisting of drug receptors, transmitter receptors, autocoid receptors, cytokine receptors, antibodies, antibody fragments, molecular recognition units, engineered antibodies, antibody mimics, adhesion molecules, agglutinins, integrins, selectins, nucleic acids and biopolymers

comprising nucleotides, saccharides, fatty acids, phenols, phosphates, sulfates, other organic monomers or nonbiologic monomers, wherein said synthetic receptors are selected by at least one of combinatorial selection, screening and selection of antibodies, engineered antibodies, oligonucleotides or oligosaccharides, or in vitro evolution, and wherein said selected drugs bind to the selected synthetic receptors with lower affinity than to the drugs' pathophysiologic receptors;

(b) specifically binding the selected drugs to the selected synthetic receptors ~~to produce~~ so that a multi-prodrug complex is produced, said multi-prodrug complex comprising the selected drugs and the selected synthetic receptors specifically bound via a saturable, noncovalent interaction between the selected drugs and the synthetic receptors that can be competitively inhibited by structural analogs of the selected drug; and

(c) administering the multi-prodrug complex to an organism so that the selected drugs dissociate from the synthetic receptors and bind to the drugs' pathophysiologic receptors.